T Cell Gene Therapy Corrects Humoral and Cytotoxic Defects in X-Linked Lymphoproliferative Disease (XLP)

Authors
Neelam Panchal[1], Ben Hougton[1], Begona Diez[1], Adrian J. Thrasher[1,2], H. Bobby Gaspar[1,2], **Claire Booth**[1,2]

[1]Molecular and Cellular Immunology Section, UCL GOSH Institute of Child Health, London, United Kingdom,[2]Department of Paediatric Immunology, Great Ormond Street Hospital, London, United Kingdom

Abstract
X-linked lymphoproliferative disease (XLP) arises from mutations in the *SH2D1A* gene encoding SAP, an intracellular adaptor protein expressed in T, NK and NKT cells. SAP is a key regulator of immune function and deficiency causes abnormalities of NK cell cytotoxicity, NKT cell development and T cell dependent humoral function. The absence of SAP in $CD4^+$ T follicular helper (T_{FH}) cells leads to defective long-term humoral immunity. Clinical manifestations are characterised by haemophagocytic lymphohistiocytosis (HLH), lymphoma and dysgammaglobulinaemia. Curative treatment is limited to allogeneic haematopoietic stem cell transplant with outcome reliant on a good donor match. We have previously shown correction of cellular and humoral immune defects in a $SAP^{-/-}$ mouse model using lentiviral mediated gene correction in haematopoietic progenitors providing proof of concept for gene therapy as a potentially curative treatment. Given that the majority of symptoms arise from defective T cell function, we also investigated whether the infusion of gene corrected T cells could correct known effector cell defects associated with the condition. We initially confirmed that transfer of wild type T lymphocytes into $SAP^{-/-}$ mice improves humoral defects characterised in this model. Subsequently CD3+ lymphocytes from $SAP^{-/-}$ mice were transduced with a gammaretroviral vector containing codon optimised human SAP cDNA before infusion into sub-lethally irradiated $SAP^{-/-}$ recipients. Animals were challenged 8-10 weeks post- infusion with the T cell dependent antigen NP-CGG and analysis performed after 10 days. We demonstrated significant improvement in germinal centre formation and NP-specific antibody responses with 20-40% engraftment of gene modified T cells. Using a SIN-lentiviral construct with codon optimised SAP transgene expression driven by the constitutive EFS promoter, we efficiently transduced XLP patient T cells resulting in improved cytotoxicity and T_{FH} cell function in vitro. In addition, using an LCL lymphoma model in NSG mice we demonstrated that adoptive transfer of gene corrected patient CTLs reduced tumour burden. Overall this data supports the further development of an autologous gene corrected T cell approach, which may offer an alternative therapeutic option for patients with XLP.